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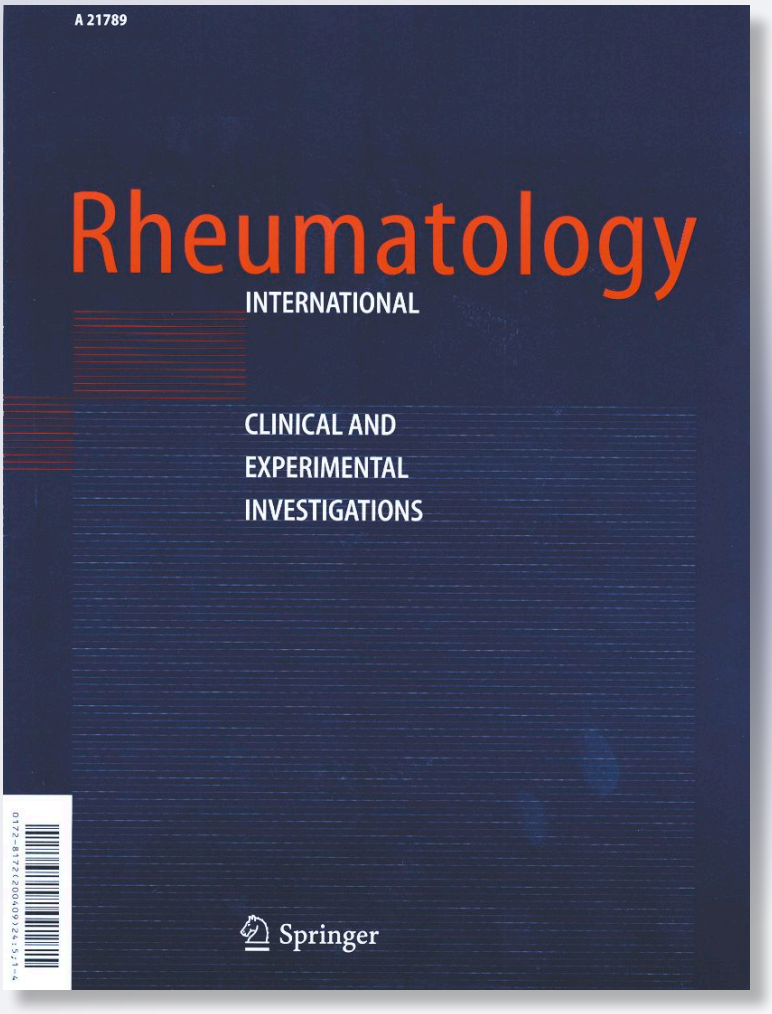

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SHORT COMMUNICATION

Infection-associated haemophagocytic lymphohistiocytosis: a case series using steroids only protocol for management

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Abstract Haemophagocytic lymphohistiocytosis (HLH) is a heterogeneous group of clinical syndromes characterised by activation and subsequent uncontrolled non-malignant proliferation of T lymphocytes and macrophages, leading to a cytokine storm that accounts for most of its clinical features such as acute febrile illness, hepatosplenomegaly, multi-organ dysfunction and fulminant pancytopenia-resembling severe sepsis. Here, we present a series of 23 cases of infection-associated HLH diagnosed in our hospital within a time period of last three and half years. Though the presentation and progression of disease was variable, the patients shared some common features like prolonged fever unresponsive to broad spectrum antibiotics, organomegaly and cytopenias. In most of the cases, however, the triggering infectious agent could not be identified. They were treated using a steroid only protocol along with supportive measures and showed an excellent response.

Keywords Infection-associated haemophagocytic syndromes · Steroids · Cytopenia

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Introduction

Haemophagocytic lymphohistiocytosis (HLH) or haemophagocytic syndromes though seemingly uncommon is not very rare [1]. It is a disorder of the mononuclear phagocytic system, characterised by uncontrolled non-malignant activation and proliferation of benign histiocytes, i.e., T lymphocytes and macrophages, causing dysfunction of various organs [2]. The Familial variety is an autosomal recessive disorder, typically having its onset during infancy or early childhood and usually fatal if untreated [3]. On the other hand, secondary HLH which is the more common variety usually results from infection, malignancy or rheumatological/connective tissue disorders. Typhoid, tuberculosis, malaria, kalaazar, Epstein–Barr virus, histoplasmosis and Human Immunodeficiency Virus have all been reported to trigger off secondary HLH [2]. A high index of suspicion is needed to promptly diagnose this potentially life-threatening condition which has a good outcome if treated timely and appropriately.

Materials and methods

Clinical records of children aged below 15 years admitted at the Institute of Child Health, Kolkata, during the time period of December 2007 to July 2010 were reviewed. The diagnosis of HLH was based on the criteria laid down by the Histiocytic Society—The Revised Diagnostic Guidelines for HLH—2004 (Table 1). The data collected included details of family history, clinical and laboratory features, treatment and outcome. Although definite infective aetiology could be labelled in only eight patients, on account of absence of family history or rheumatological disorders, no recurrence on stopping treatment, nor any infantile onset of disease was observed; the diagnosis was

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Table 1 Revised diagnostic guideline for HLH (4)

The diagnosis of HLH can be established if one of either 1 or 2 below is fulfilled
Molecular diagnosis consistent with HLH
Diagnostic guidelines of HLH fulfilled [five out of eight criteria (*) below]
Initial diagnostic criteria (to be evaluated in all patients of HLH and malignancy to be excluded)
*Fever
*Splenomegaly
*Cytopenias (affecting two or more cell lineages of peripheral blood)
Haemoglobin < 90 gram/l (in infants < 4 weeks: Hb < 100 gram/l)
Platelets < 100 × 10 9/l
Neutrophils < 1 × 10 9/l
*Hypertriglyceridemia and/or hypofibrinogenemia
Fasting triglyceride ≥ 3.0 mmol/L (i.e. ≥265 mg/dl)
Fibrinogen ≤ 1.5 gram/L
*Haemophagocytes in bone marrow or spleen or lymph nodes
New diagnostic criteria
*Low or absent NK cell activity (according to local laboratory reference)
*Serum ferritin ≥ 500 microgram/dl
*Soluble CD25 (i.e. soluble IL-2 receptors) ≥ 2,400 U/ml
Exclusion criteria: no evidence of malignancy

labelled as infection-associated HLH (IAHLH). Once diagnosed, the children were treated with dexamethasone only along with supportive therapy. The dosing of dexamethasone was as per HLH 2004 protocol but in contrast to HLH 2004 protocol, no patient received any other chemotherapy or immunotherapy.

Nineteen children out of 23 are on regular follow-up and have remained asymptomatic.

Appropriate ethical approval was obtained from the Ethical Committee Institute of Child Health, Kolkata.

Results

Clinical features

Twenty-three patients including 13 boys and 10 girls fulfilled the criteria of IAHLH. The frequency worked out to be 1.15 per 1,000 hospital admissions. The age at presentation ranged from 2 months to 15 years with a median age of 7 years. In no case, there was a positive family history. The interval between onset of symptoms and diagnosis of HLH varied from 8 days to 1 month. Fever more than 7 days and organomegaly (hepatosplenomegaly or splenomegaly or hepatomegaly) were present in all the cases. Anaemia (Hb < 9 gm%) was present in 21 patients (91.3%), 9 had bleeding manifestations (39.1%). Twelve patients presented with lymphadenopathy (52.1%), 17 presented with skin rash or mucosal involvement (73.9%) and 4 patients had complaints of joint pain but only 2 had arthritis (8.6%). Central Nervous System involvement was present in 14 patients (60.8%), cardiac in 9 (39.1) and renal in 5 (21.7%) (Table 2).

Table 2 Clinical characteristic of the cohort

Clinical parameters	Total no. of patients (23)	Percentage
Family history	0	0
Fever	23	100
Joint pain	3	15.7
Rash	14	73.7
Hepatomegaly	15	78.9
Splenomegaly	16	84.2
Bleeding manifestations	7	36.8
Lymphadenopathy	11	57.9
CNS involvement	12	63.2
Skin/mucosal involvement	16	84.2
Arthritis	2	10.5
Renal involvement	4	21
Cardiac involvement	8	42

Laboratory features

The laboratory features (Table 3) of all these 23 patients were quite typical. Anaemia (Hb < 9 gm%) was noted in 21 patients (91.3%), thrombocytopenia (platelet < 1,00,000) in 19 (82.6%) and neutropenia (ANC < 1,000) in 13 (56.51%). Hypertriglyceridemia (≥265 mg/dl) was present in 21 patients (95.4%). Fibrinogen estimation was available in only 15 patients, of which 12 showed a low value (i.e. <1.5 g/L). Elevated ferritin was noted in all except one child (95.6%). Bone marrow aspiration was done in all patients of whom 18 showed evidence of haemophagocytosis (78.2%). Infection screening revealed Leishmaniasis, Hepatitis A, Chikungunya, Tuberculosis, Cytomegalovirus as the inciting factor in five patients, two had Dengue and another three were positive for Epstein–Barr Virus infection. We could not do NK cell activity or CD 25 level due to unavailability of equipped laboratory facility.

Treatment and outcome

The children were given supportive therapy in the form of blood component transfusions as and when required along with broad spectrum antibiotics. Definitive therapy was administered in the form of parenteral steroid as dexamethasone (10 mg/m^2 in 3–4 divided doses/day). After the fever

Table 3 Laboratory findings of the cohort

Laboratory parameters	Total no. of patients	Percentage
Anaemia (Haemoglobin < 9 gm%)	21	91.3
Neutropenia (ANC < 1000)	13	56.51
Thrombocytopenia (Plt < 1,00,000)	19	82.6
Raised SGPT	18	78.2
Falling ESR	15	65.21
Increased CRP	19	82.6
Raised ferritin	22	95.6
Raised LDH ($n = 20$)	18	90
Raised d-dimer ($n = 20$)	18	90
Raised triglyceride ($n = 22$)	21	95.4
Raised lipase ($n = 14$)	9	64.2
Decreased fibrinogen ($n = 15$)	12	80
Haemophagocytes in bone marrow	18	78.2
Diagnosed offending infection	10	43.4

subsided, parenteral steroids were switched over to oral dexamethasone in the same dose and gradually tapered off over a period of 8 weeks maintaining the HLH 2004 protocol. In 84% cases, fever subsided within 48–72 h of starting steroids, reversal of cytopenias and regression of hepatosplenomegaly occurred over the next 7–10 days. Serum ferritin started normalising within a week. We lost only one patient of disseminated CMV infection with HLH. Nineteen patients are on regular follow-up and stable without any recurrence of the disease. No chemotherapeutic agent other than steroids was used in all of our 23 patients.

Discussion

Infection-associated HLH usually occurs due to immune up regulation following a triggering infection. The aim of this article is to describe the clinical and laboratory features of IAHLH, to share our experiences in dealing with such cases with the novel "Steroid Only Protocol" and to sensitise the paediatricians and intensivists to this not so uncommon problem to facilitate early diagnosis and adequate treatment.

The specific infections are often tough to identify and are usually thought to be viral in nature [4]. Similar to the study by Ramachandran et al., infectious aetiology could be identified by us in only about 40% cases [5].

The typical features of IAHLH are fever and hepatosplenomegaly, but similar to our series, they often have multiorgan involvement [6]. In accordance with previous studies, the most common laboratory finding in our series was also cytopenia (at least two peripheral cell lines being depressed) followed by hyperferritinemia [7] and hypertriglyceridemia. Fibrinogen level was reduced in 80% of children in whom it was measured. The strongest evidence for HLH is the presence of haemophagocytes in the bone marrow which was demonstrated in 79% of cases which compares favourably with the 84% incidence reported by Ramachandran et al. [5]. It should be remembered that absence of histological proof should not be a deterrent for the initiation of therapy, and a strong clinical suspicion coupled with positive laboratory parameters is often enough to start therapy [8].

In the HLH2004 protocol, three tier therapies have been advocated. At initiation, all patients irrespective of type and aetiology are started on dexamethasone, etoposide and cyclosporin A. In addition, some of the selected patients will receive intrathecal therapy with methotrexate and prednisolone. In contrast, our patients received only dexamethasone as chemotherapy. "Steroid only" protocol in HLH has rarely been reported in literature. Ramachandran et al. [5] recently reported success in two-third cases of HLH with a combination of steroid and intravenous immunoglobulin, whereas almost all children in our cohort of IAHLH responded to the "steroid only" protocol without any significant mortality.

Though traditionally perceived as a near fatal disease requiring aggressive chemotherapy, our patients did remarkably well with the use of only corticosteroids and supportive therapy without necessitating the use of further chemotherapy. This is in contrast to the HLH 2004 guidelines where intensification of chemotherapy has been advocated, but the Histiocytic Society guidelines were laid down primarily for the familial variety of disease. Observing this response to a corticosteroid only protocol, we propose that a steroid only treatment for infection-associated HLH can be a good alternative particularly in resource-constrained environment where financial constrains prevent routine use of IVIG. Our study does have the usual fallacies associated with any retrospective study and definitely further prospective studies are required to substantiate our findings.

What is known HLH is a fatal disease requiring aggressive chemotherapy.

What does this study adds In infection-associated HLH syndrome, a "steroid only" protocol along with supportive therapy may be advocated.

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